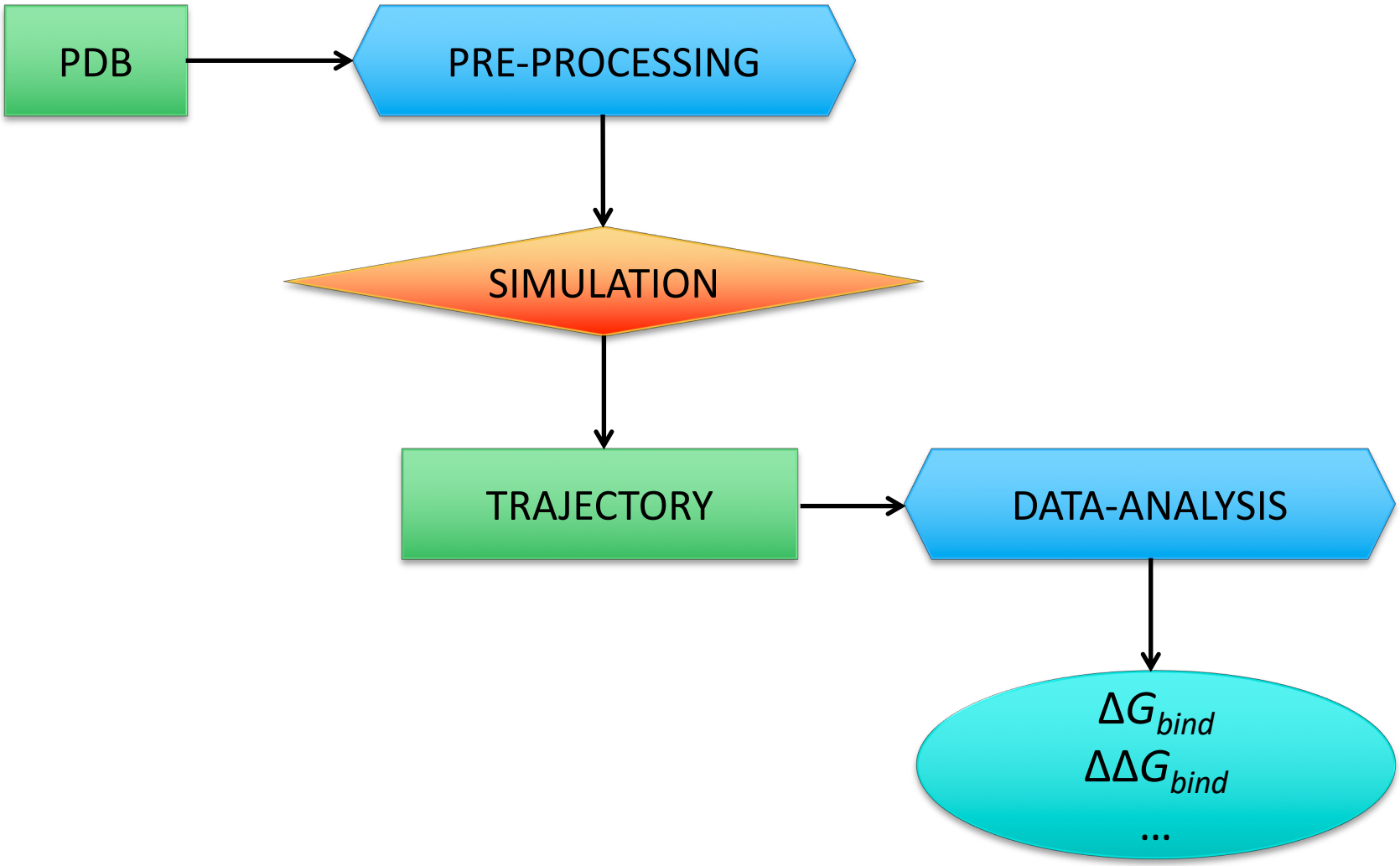
“STANDARD” MD

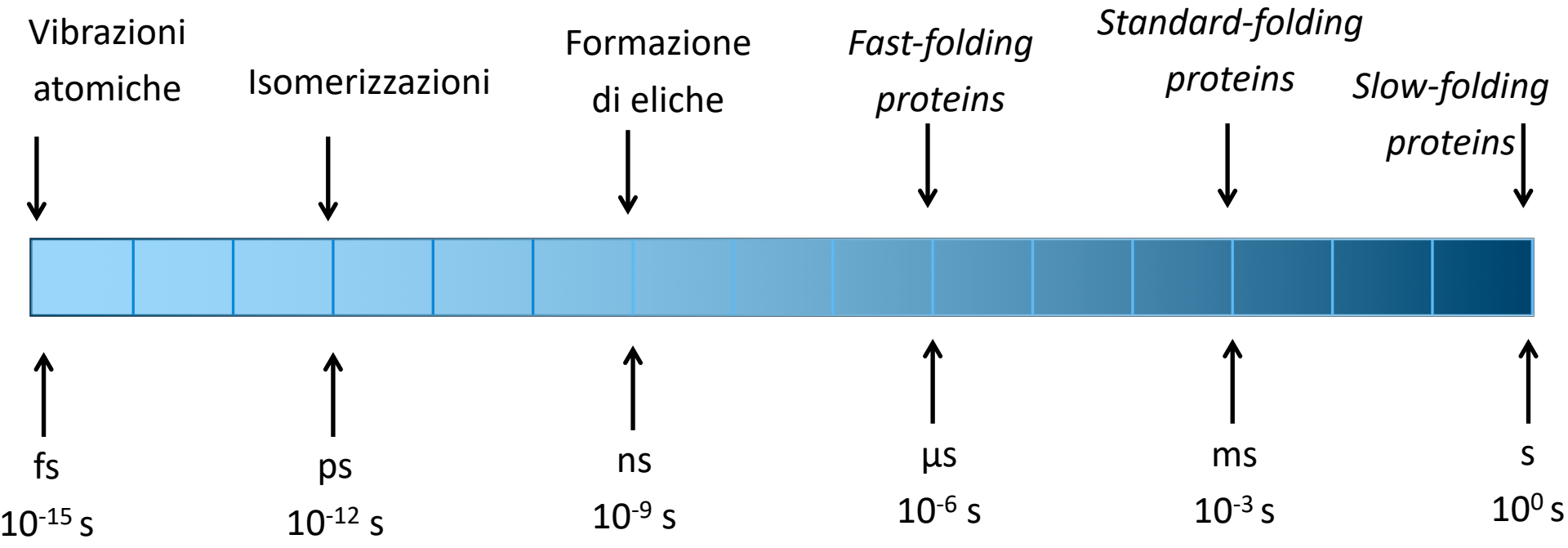

PDB
PRE-PROCESSING
SIMULATION
TRAJECTORY
DATA-ANALYSIS
ΔG_{bind}
$\Delta\Delta G_{bind}$
...

But what if we want more???

MATH-“FREE” slides,

qualcuno di cui ci fidiamo garantisce ☺

Timescale


Vibrazioni atomiche
Isomerizzazioni
Formazione di eliche
Fast-folding proteins
Standard-folding proteins
Slow-folding proteins
fs
10-15 s
ps
10-12 s
ns
10-9 s
µs
10-6 s
ms
10-3 s
s
100 s

So, we want more…

Non è possibile iniziare lo step N+1 finché non abbiamo finito N, N-1…

Ad ogni step molti dati devono essere inviati a tutti i processori/nodi,

è necessaria una interconnessione molto efficente!

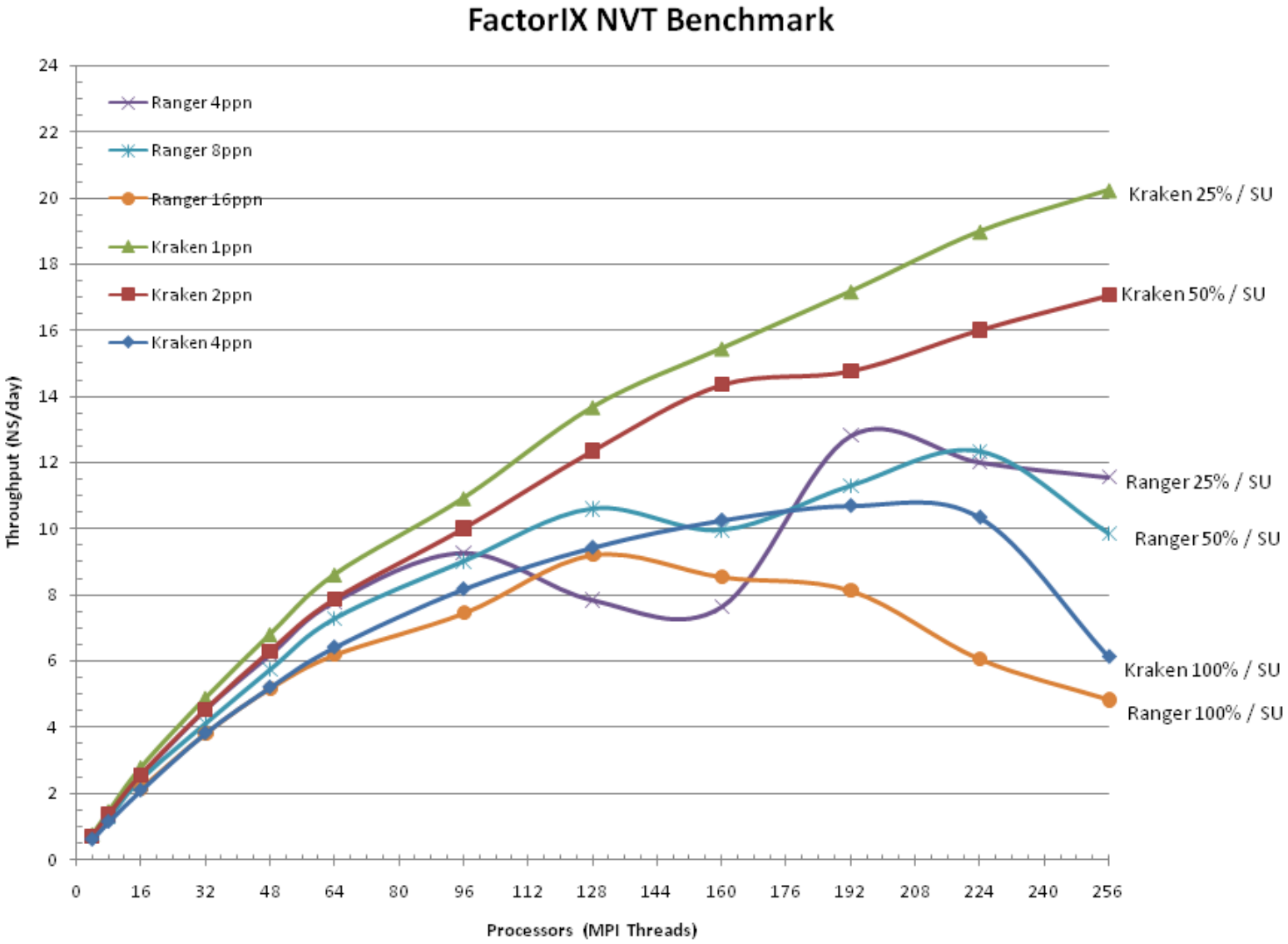
PS: usare più CPU non è sempre la scelta più veloce…

La scalabilità è problema-specifica!

Scaling

Ranger: ogni nodo ha 4 Quad Core AMD 2.3 GHz, SDR Infiniband interconnect

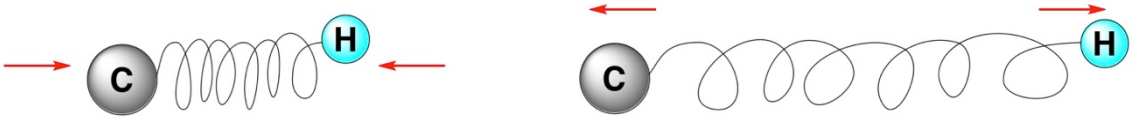
Kraken: ogni nodo ha 1 Quad Core AMD 2.3 GHz, Cray CStar2 interconnect



SHAKE & Hydrogen Mass Repartitioning

In MD il *timestep* (δt) è determinato dai movimenti più rapidi presenti!

…stretching dei legami coinvolgenti gli atomi leggeri, H ⟶ 1 fs

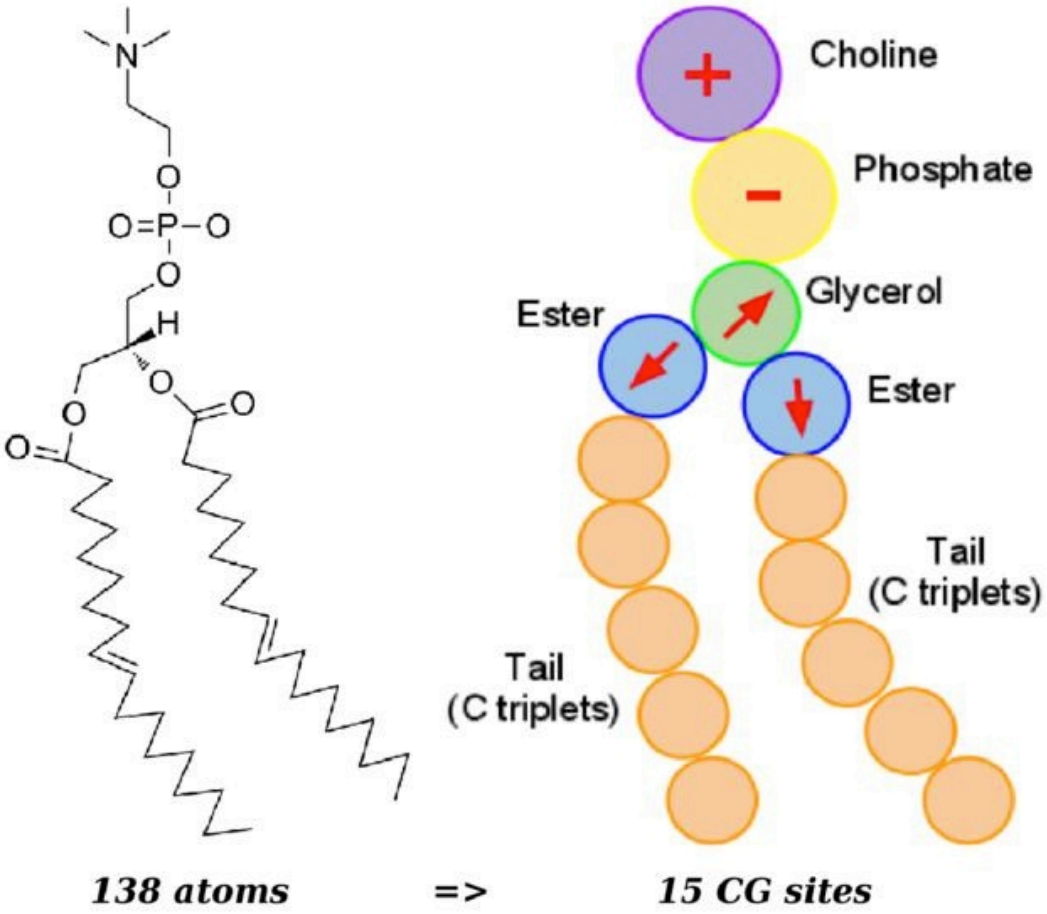


- **L'algorismo SHAKE** applicato ai legami che coinvolgono H ne "limita" la mobilità, consentendo di portare il δt a 2 fs.

- **Hydrogen Mass Repartitioning**:

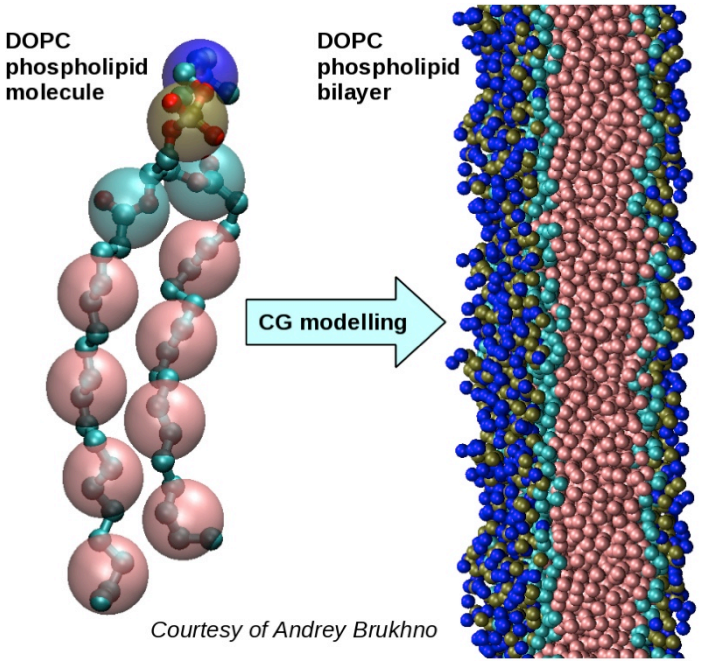
R-CH_2-R	(H ≈ 1) *2	C ≈ 12	tot ≈ 14
R-CH_2-$R_{repartitioned}$	(H ≈ 3) *2	C ≈ 8	tot ≈ 14

Coarse-grained MD



3 atoms => 1 CG site

32 850 => 10 950

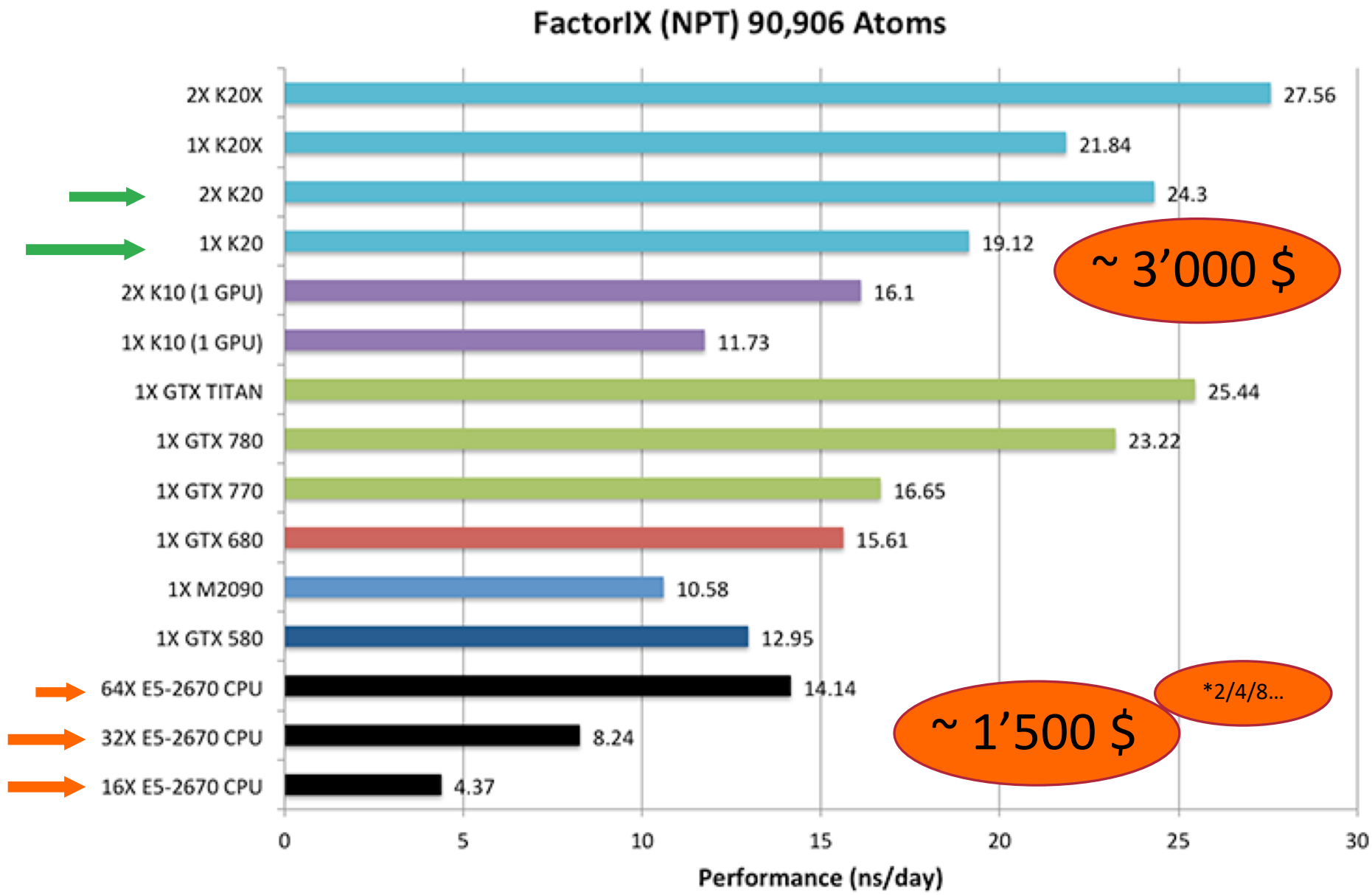


Courtesy of Andrey Brukhno

We want even more

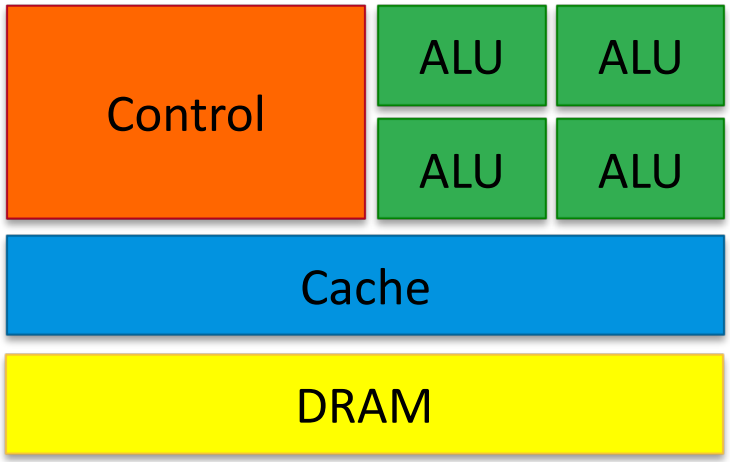
Graphic Processing Unit (GPU)

- Processore specifico per accelerare il rendering in computer-graphic
- Sviluppo guidato da un'industria videoludica da 150 $*10^9$ $...
    - NSF 7 $*10^9$ $, NIH 30 $*10^9$ $...
- In constante e rapido sviluppo!
- Prezzo & **consumo**, a parità di prestazioni, molto inferiori!

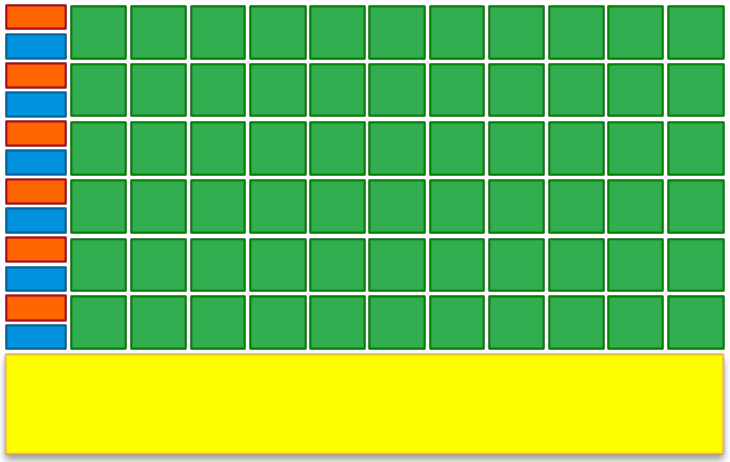

FactorIX (NPT) 90,906 Atoms
2X K20X
1X K20X
2X K20
1X K20
2X K10 (1 GPU)
1X K10 (1 GPU)
1X GTX TITAN
1X GTX 780
1X GTX 770
1X GTX 680
1X M2090
1X GTX 580
64X E5-2670 CPU
32X E5-2670 CPU
16X E5-2670 CPU
27.56
21.84
24.3
19.12
16.1
11.73
25.44
23.22
16.65
15.61
10.58
12.95
14.14
8.24
4.37
~ 3’000 $
~ 1’500 $
*2/4/8...
0
5
10
15
20
25
30
Performance (ns/day)

CPU vs GPU

CPU

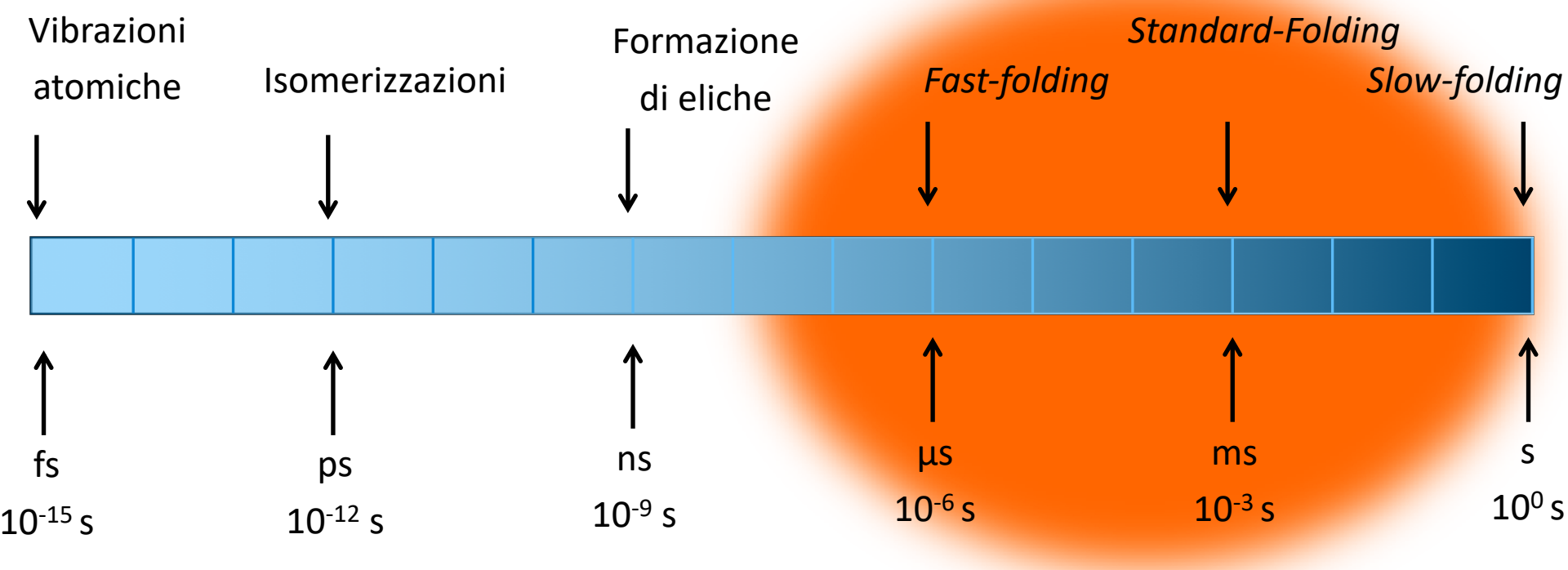


GPU



*ALU: unità aritmetico-logica

Timescale

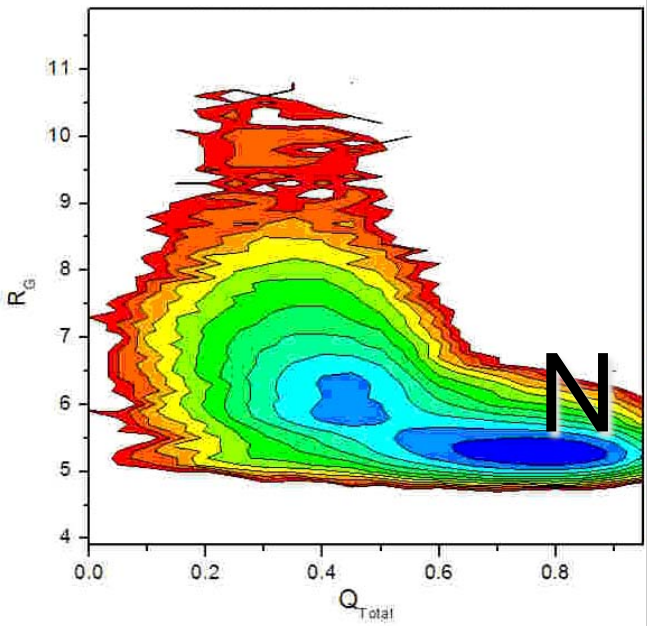

Vibrazioni atomiche
Isomerizzazioni
Formazione di eliche
Fast-folding
Standard-Folding
Slow-folding
fs
10-15 s
ps
10-12 s
ns
10-9 s
µs
10-6 s
ms
10-3 s
s
100 s

Folding

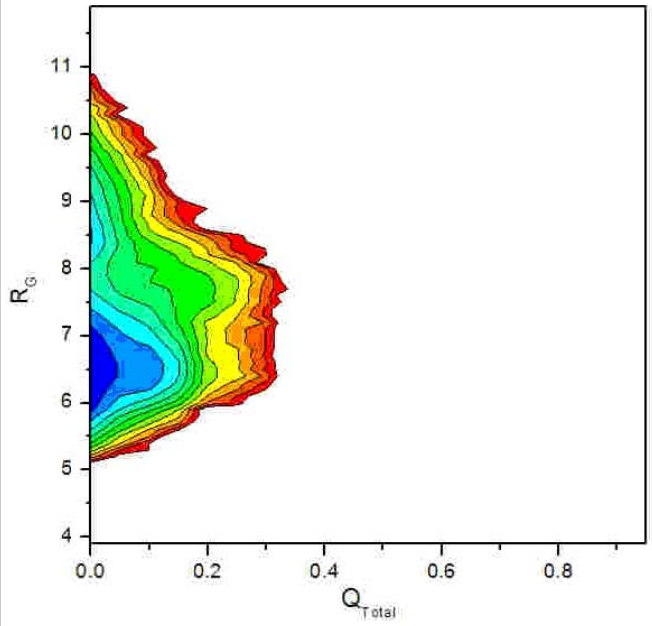
Energy landscape*, tramite MD classica

*Mappatura di tutte le possibili conformazioni di una molecola e i corrispondenti valori di energia.

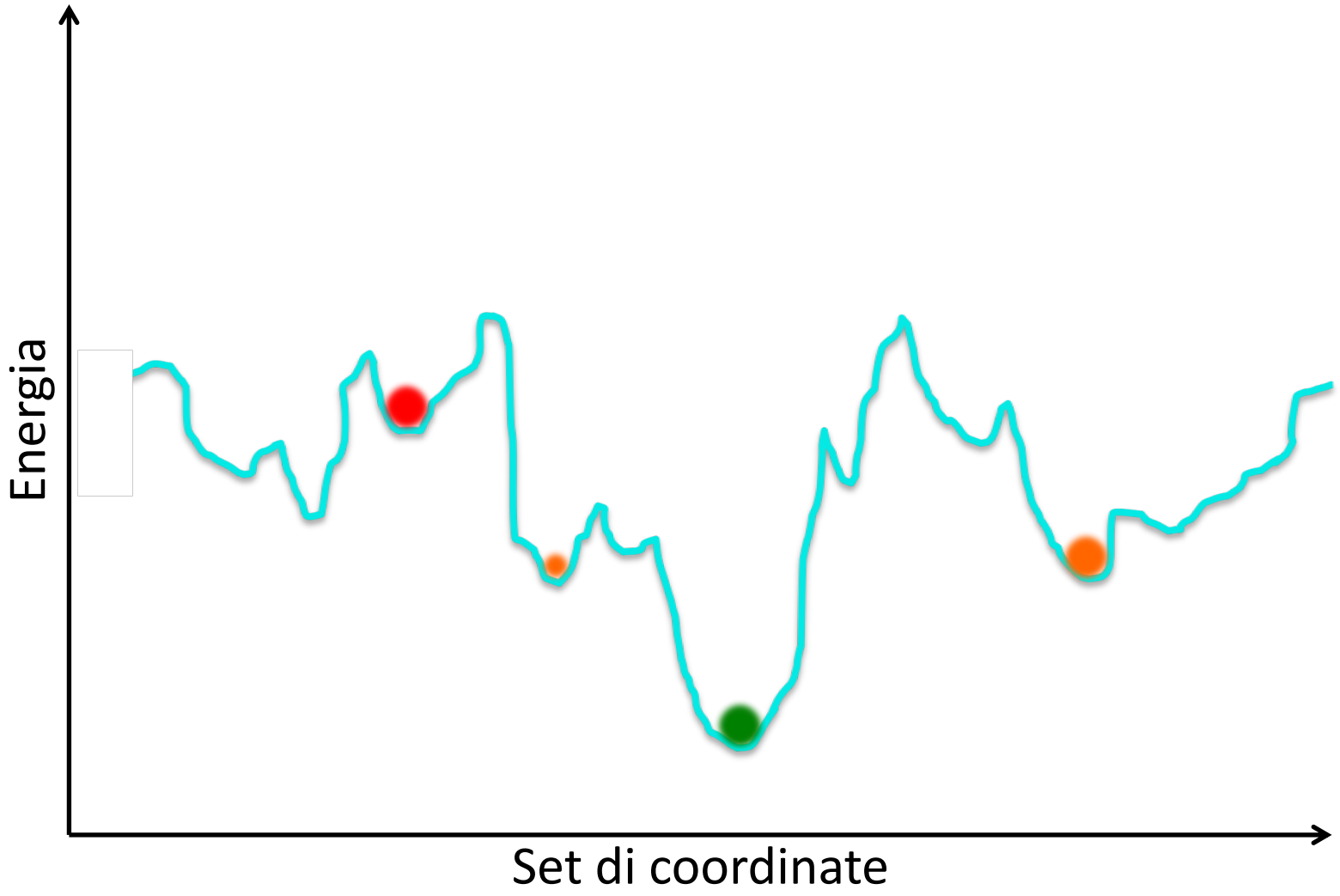
Dalla conformazione nativa
350 K



Dalla conformazione lineare
350 K



Stuck



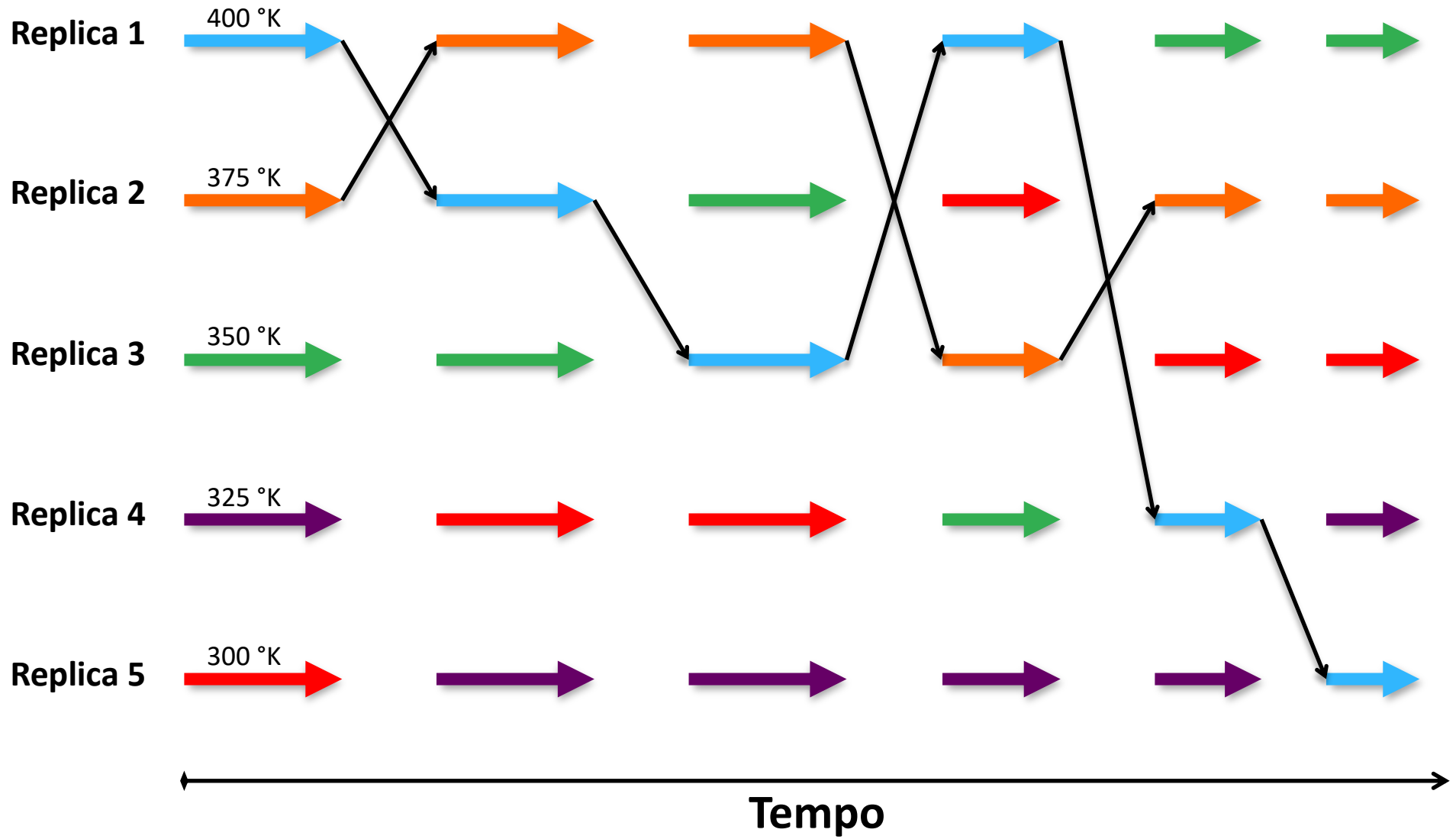
T–REMD

- Diverse repliche, a diverse temperature
  - A temperature elevate si introducono *restraint* (chiralità…)
  - Attenzione che a T>373 °K bolle l'acqua…

- Calcola la probabilità di uno scambio (esistenza delle diverse configurazioni alle diverse temperature) ad intervalli regolari:
  - se lo scambio ha successo vengono scalate le velocità (modifico solo l'E_{kin}) per raggiungere la temperatura target;

- Altamente parallelizzabile

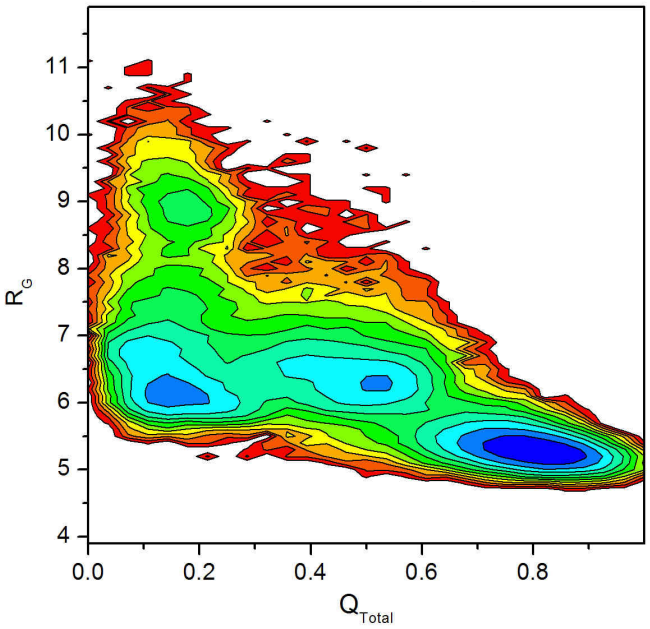
T–REMD


Replica 1
400 °K
Replica 2
375 °K
Replica 3
350 °K
Replica 4
325 °K
Replica 5
300 °K
Tempo

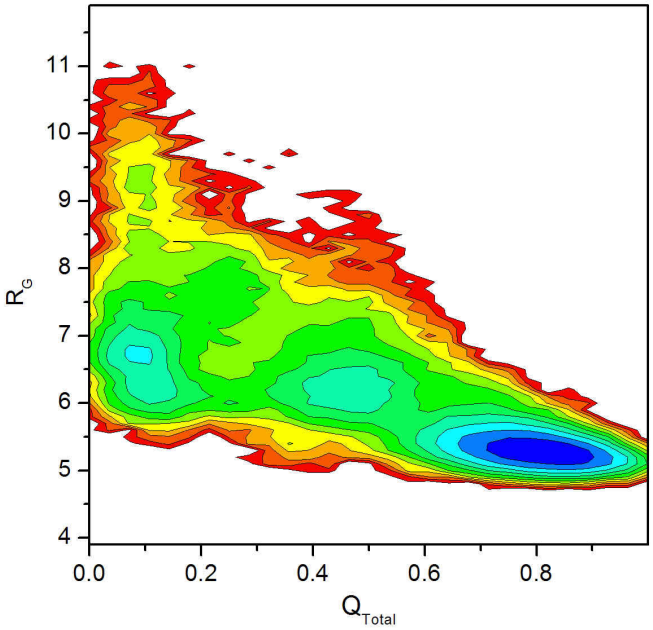
Much better

Energy surface, from T-REMD

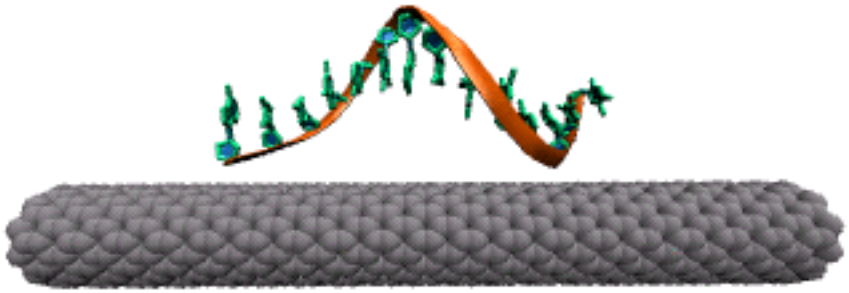
Dalla conformazione nativa
350 K

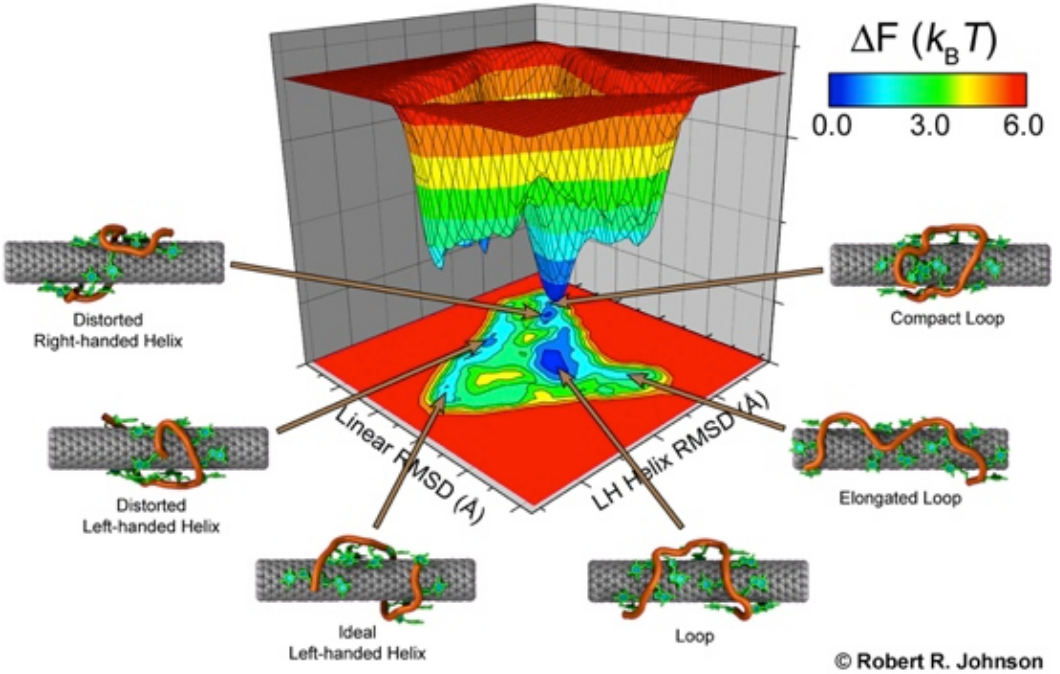


Dalla conformazione lineare
350 K

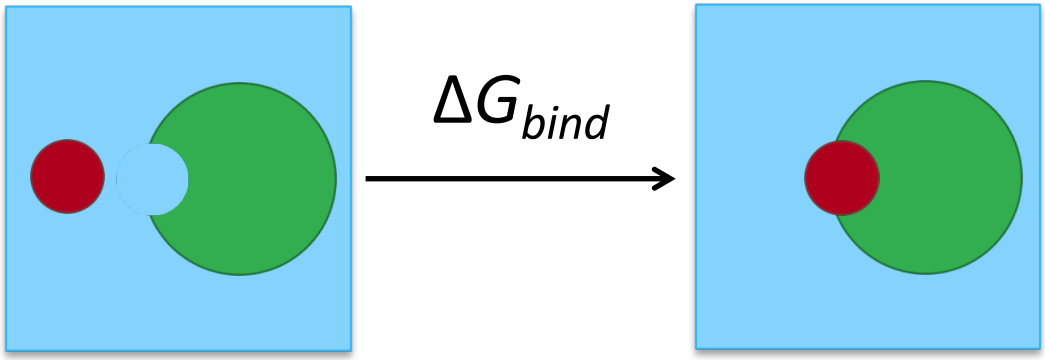


T–REMD




ΔF ($k_B T$)
0.0
3.0
6.0
Distorted
Right-handed Helix
Compact Loop
Distorted
Left-handed Helix
Linear RMSD (Å)
LH Helix RMSD (Å)
Elongated Loop
Ideal
Left-handed Helix
Loop
© Robert R. Johnson

ΔG_{bind}

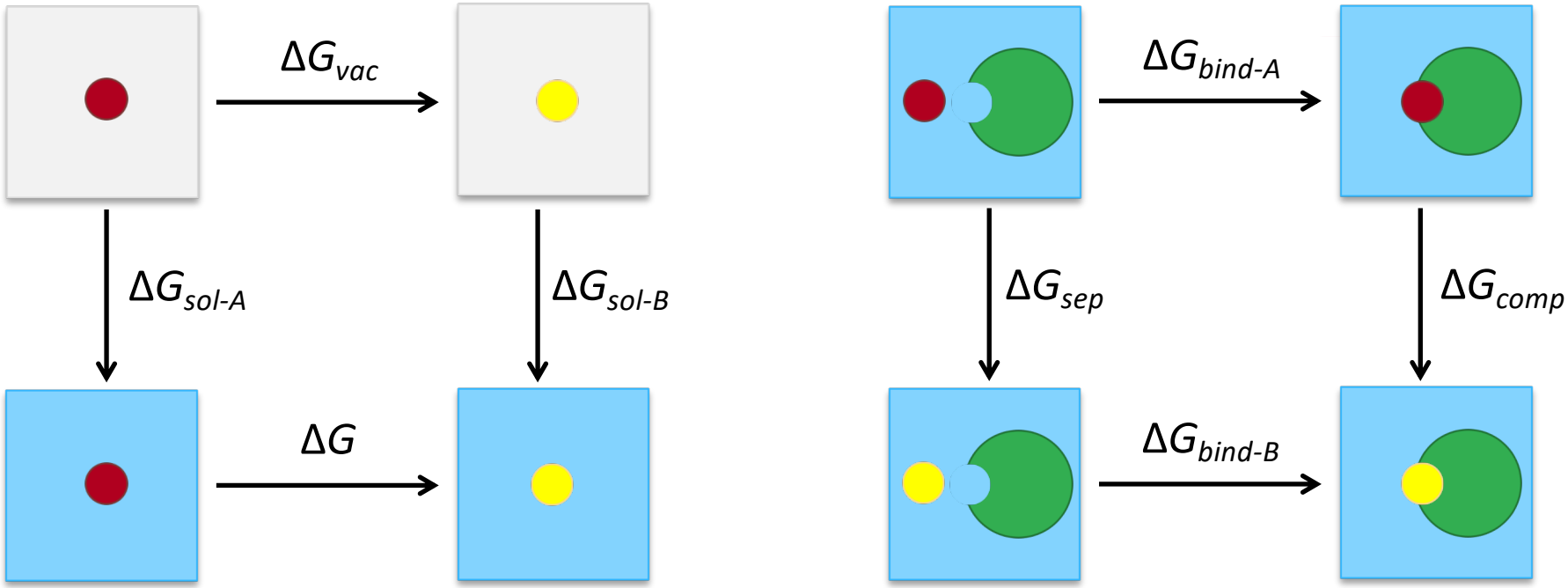


$$\Delta G_{bind} = \Delta G_{comp} - (\Delta G_{rec} + \Delta G_{lig})$$

"Corpora non agunt nisi fixata"

Paul Ehrlich, 1913

Thermodynamic Integration



Ciclo termodinamico: per ogni cliclo chiuso $\Delta G = 0$...

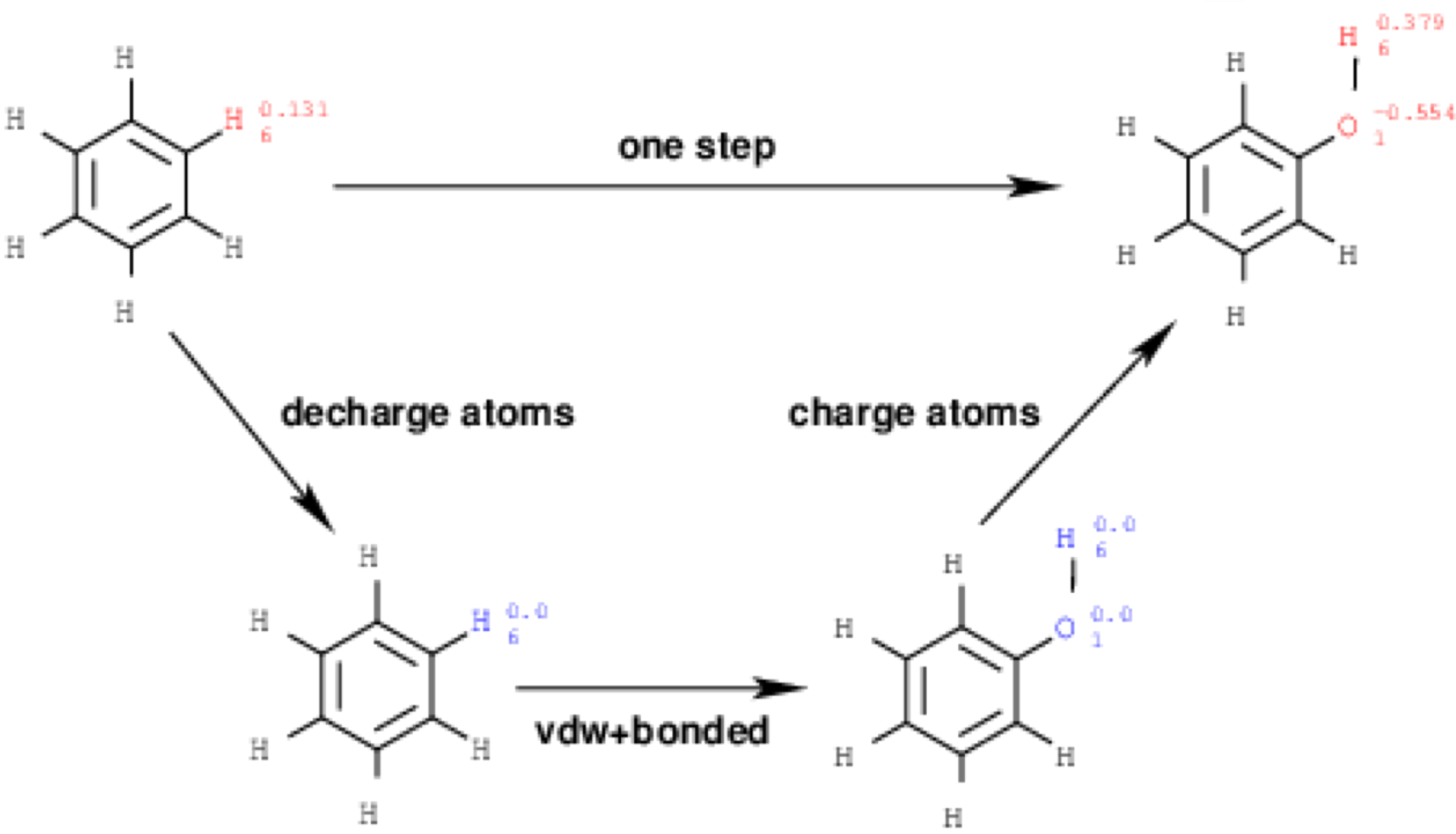
$$\Delta G_{bind\text{-}A} + \Delta G_{comp} - \Delta G_{bind\text{-}B} - \Delta G_{sep} = 0$$

Alchimia computazionale

$$H(\lambda) = [1-f(\lambda)]H_A + f(\lambda)H_B \qquad \lambda = [0,1]$$

$$m_i(\lambda) = [1-\lambda]m_i^A + \lambda m_i^B$$

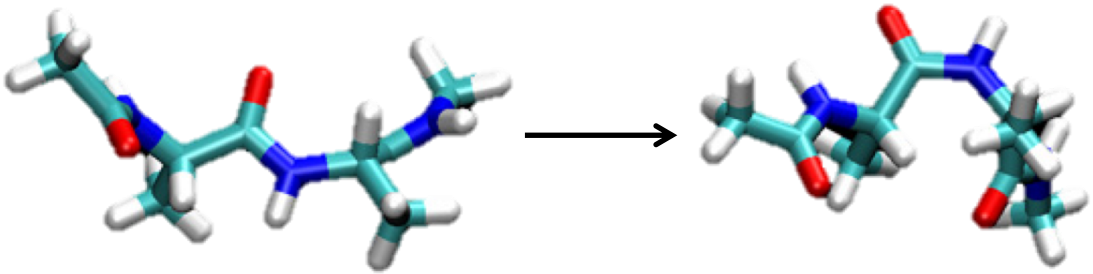
Thermodynamic Integration



Barriere energetiche

Come forzare il passaggio di una barriera energetica senza compromettere le proprietà termodinamiche?

Transizioni spontanee molto lente… non posso aspettare MD…



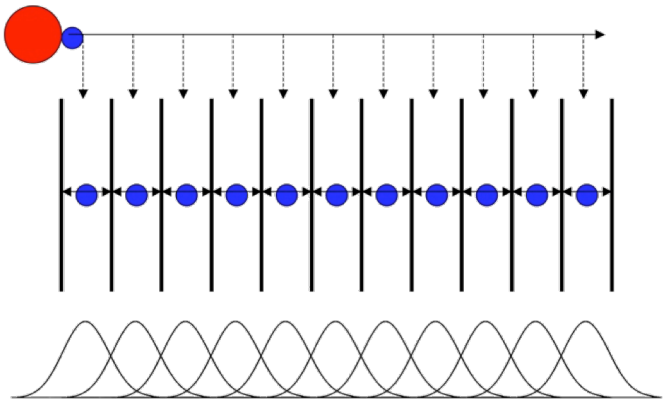
ALA-ALA-ALA isomerizzazione cis/trans

Forziamo il sistema lungo una coordinata di reazione che scegliamo!

Umbrella Sampling

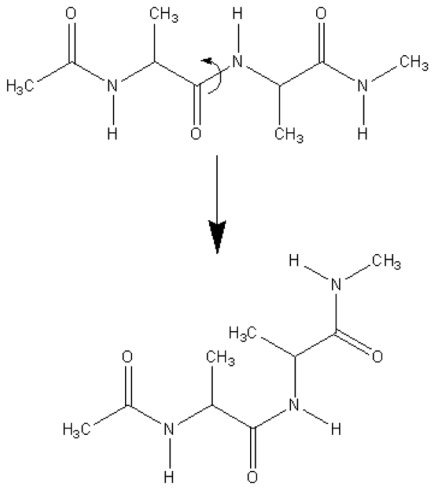
Lunga MD - adeguato campionamento dello spazio conformazionale - profilo di energia libera (FEP);

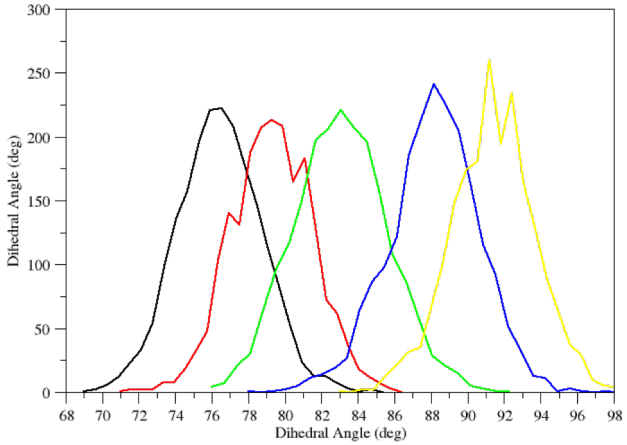
Ma anche sistemi molto piccoli necessitano di più di 1 ms di simulazione…

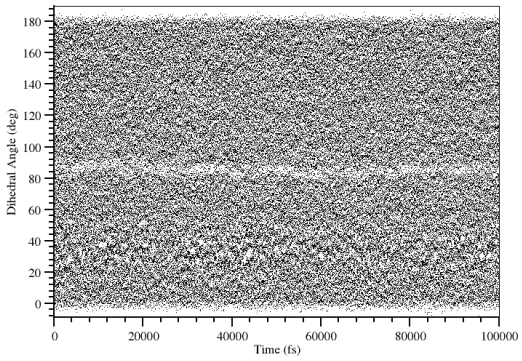


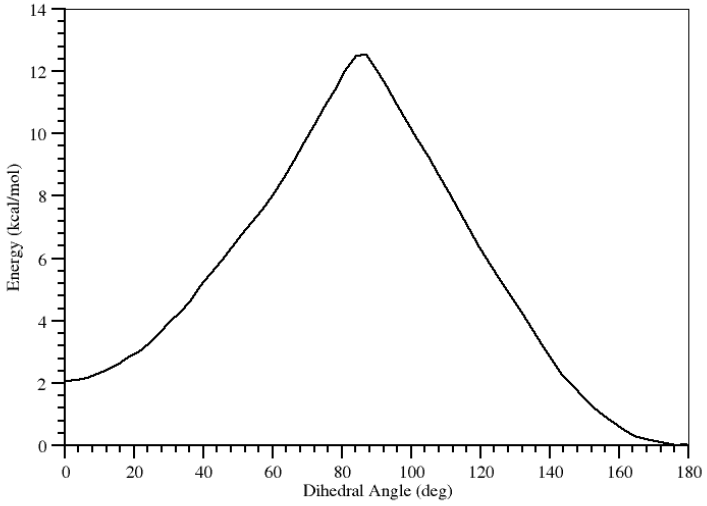
- Suddivido la transizione in una serie di “finestre”;
- Forzo il sistema vicino al centro di ogni finestra;
- Ottengo una serie di istogrammi;
- Post-processando i risultati riesco ad eliminare il bias introdotto e ricavo il FEP

Umbrella Sampling

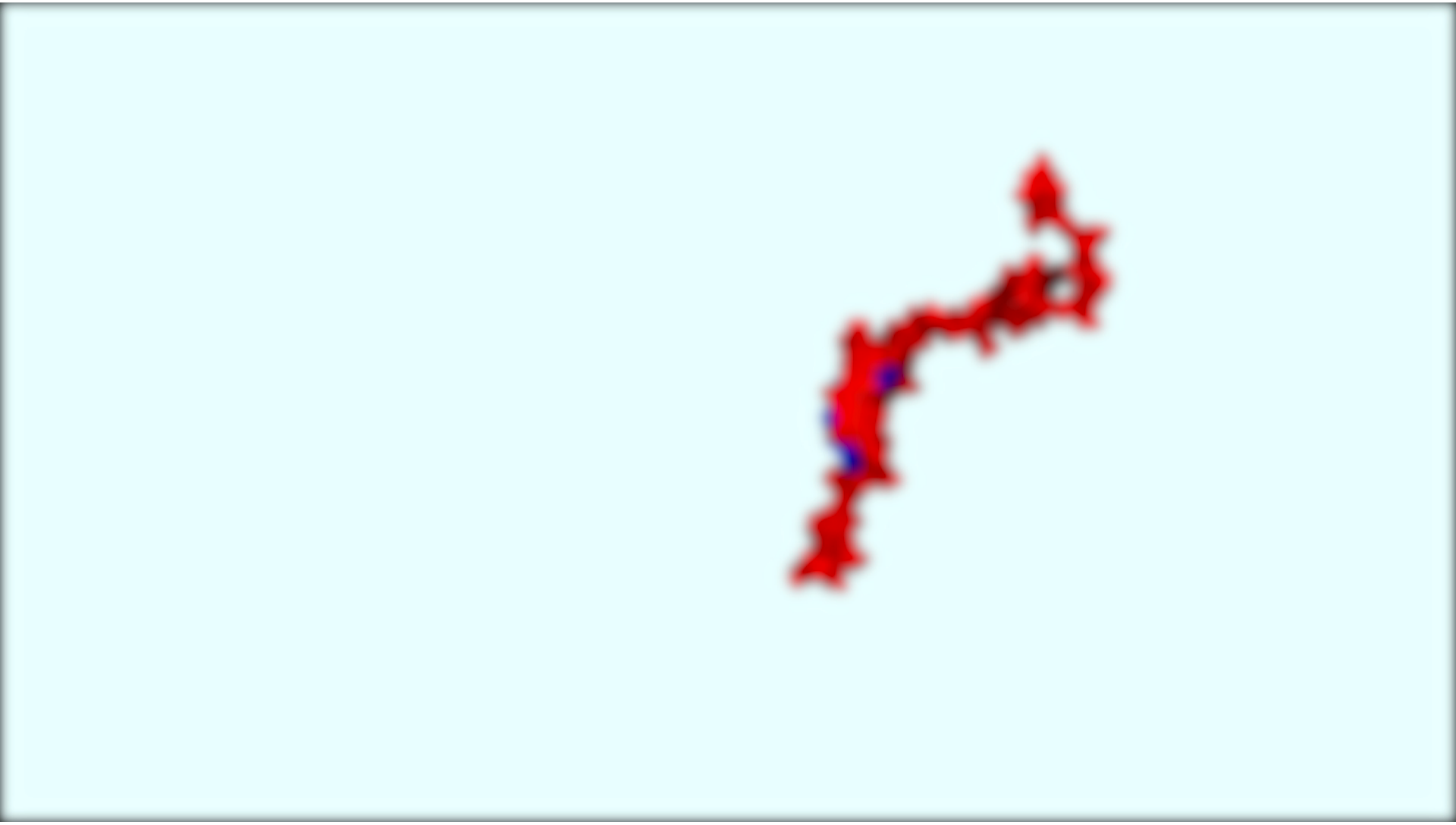








Examples



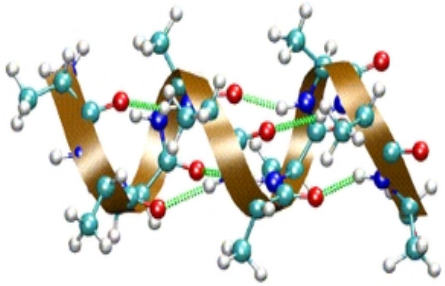
SMD: CV, Jarzynski

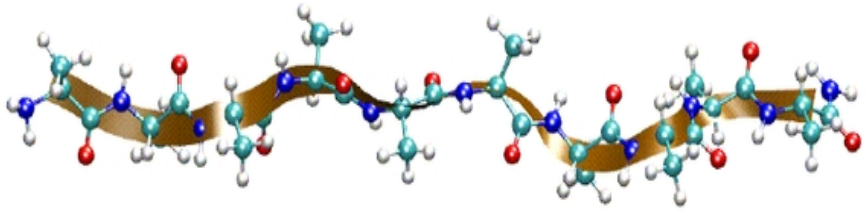
Jarzynski: la differenza di energia libera tra due stati A e B puo essere calcolata tramite

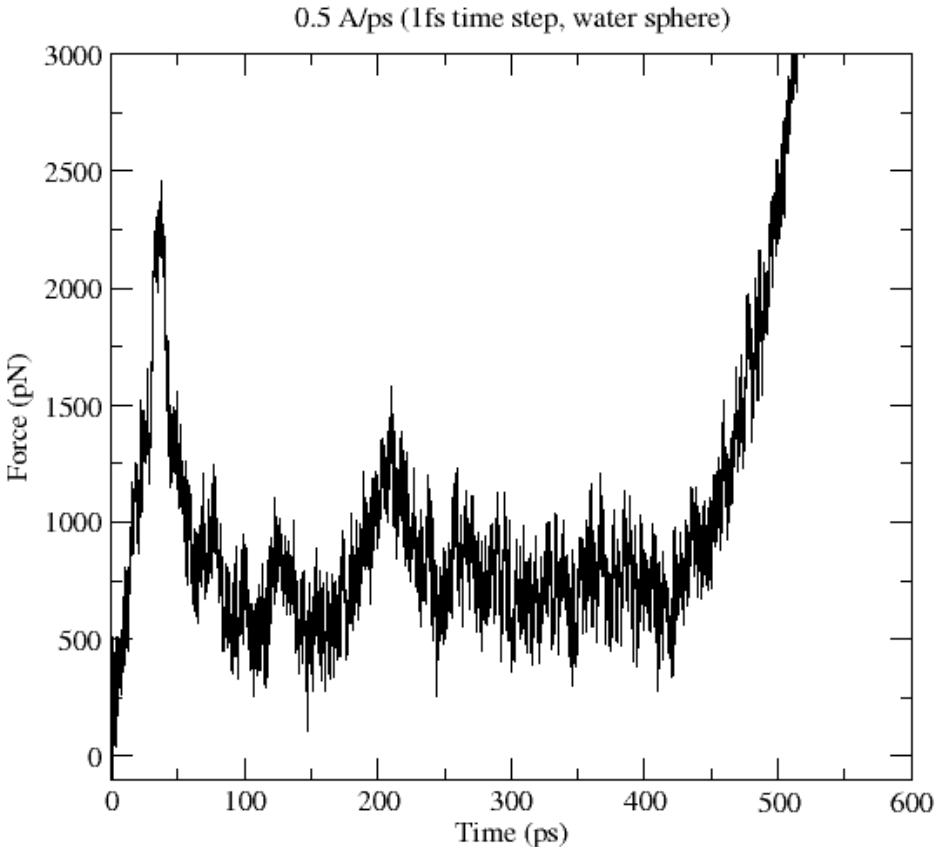
$$\exp(-\Delta G/k_B T) = \langle \exp(-W/k_B T) \rangle_A$$

Calcolo $\Delta\Delta G$ eseguendo diverse SMD partendo da diverse coordinate iniziali.

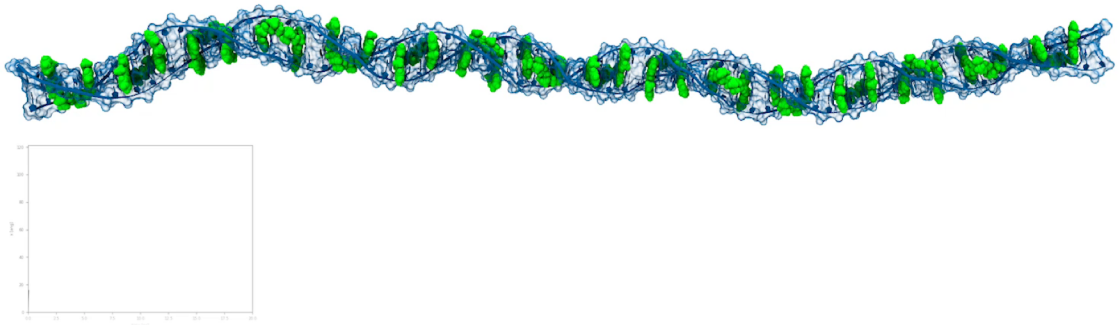
SMD: CV, H-bonds

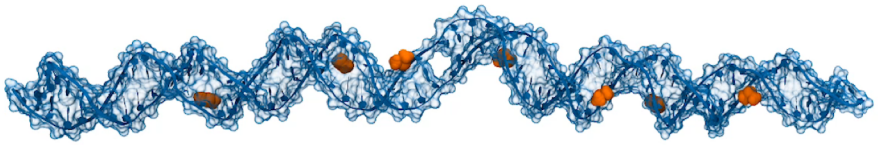


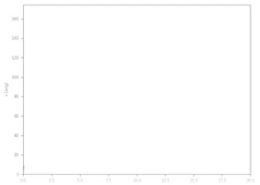


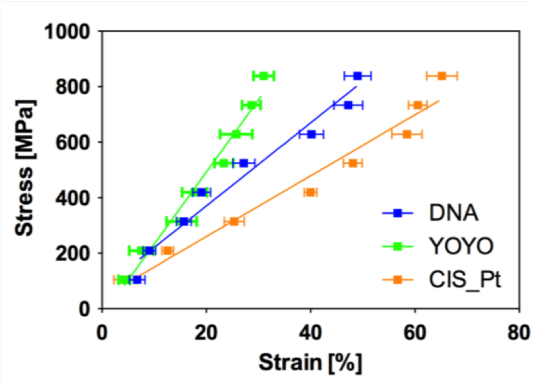


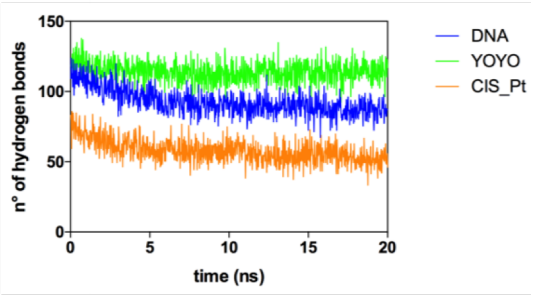
SMD: CF, mechanical properties

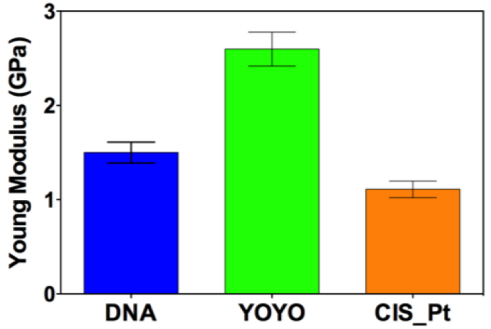




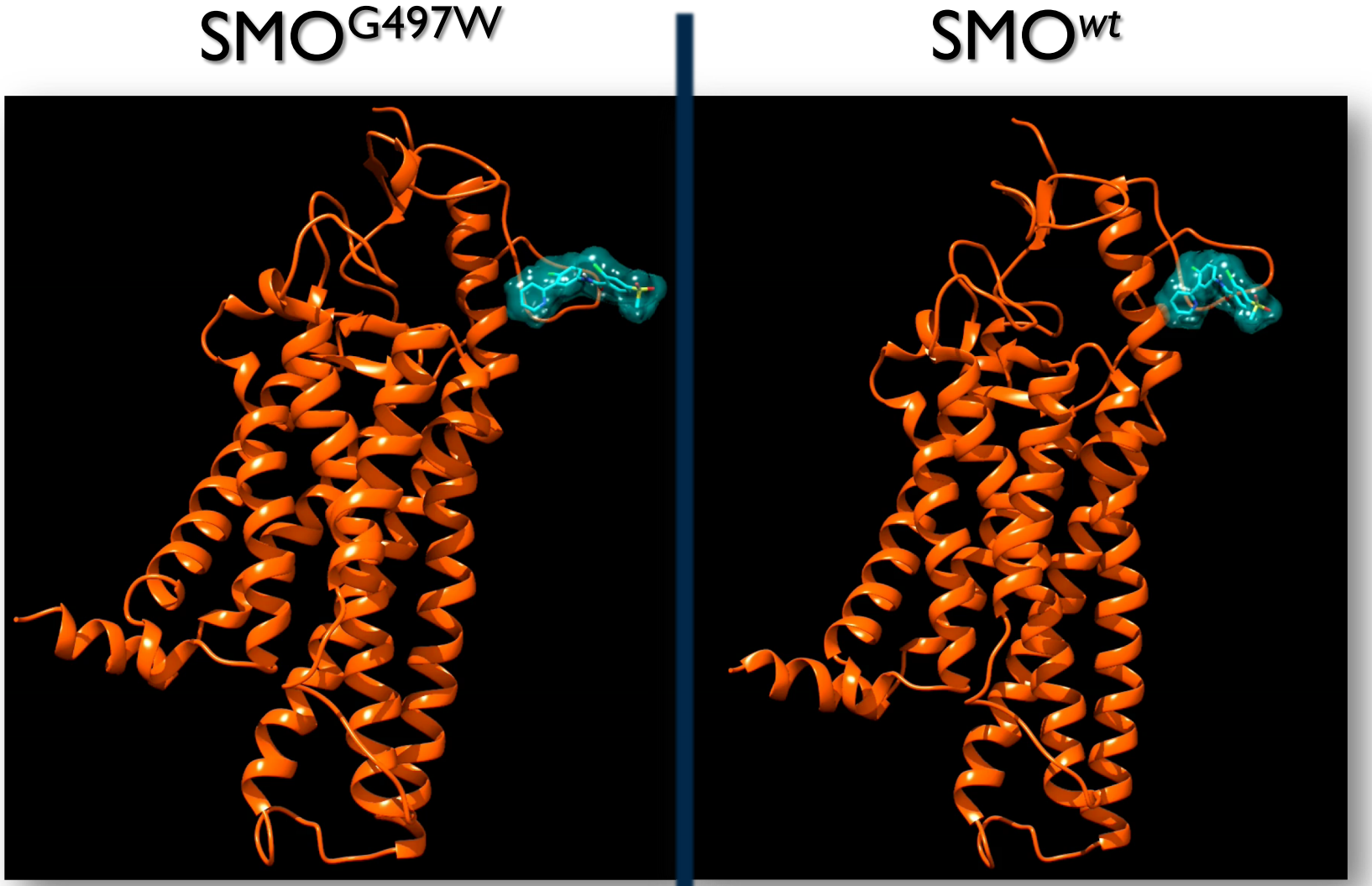








WT | MUT



Docking